CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (withdrawn) A gene cluster having open reading frames which encode polypeptides sufficient to direct the synthesis of a safracin molecule.

2. (currently amended) ~~A~~ An isolated nucleic acid sequence comprising:

a) a nucleic acid sequence SEQ ID NO:1, or variants or portions thereof encoding at least one non-ribosomal peptide synthetase which catalyses at least one step of the biosynthesis of safracins;

b) a nucleic acid sequence which is fully complementary to the sequence in a)~~;~~

~~c) variants or portions of the sequences of a) or b)~~.

3. (canceled)

4. (currently amended) The nucleic acid sequence according to claim 2, wherein the nucleic acid sequence a) ~~which~~ comprises at least one of the *sacA, sacB, sacC, sacD, sacE, sacF, sacG, sacH, sacI, sacJ, orf1, orf2, orf3* or *orf4* genes, including variants or portions thereof encoding at least one non-ribosomal peptide synthetase which catalyses at least one step of the biosynthesis of safracins.

5. (currently amended) The nucleic acid sequence according to claim 2 wherein the nucleic acid sequence a) encodes a polypeptide which is at least 30% identical in amino acid sequence to a polypeptide encoded by any of the safracin gene cluster open reading frames *sacA* to *sacJ* and *orf1* to *orf4* ~~(SEQ ID NO:1 and genes encoded in SEQ ID NO:1)~~ or encoded by a variant or portion thereof encoding at least one non-ribosomal peptide synthetase which catalyses at least one step of the biosynthesis of safracins.

6. (currently amended) The nucleic acid sequence according to claim 2, wherein the nucleic acid sequence a) ~~which~~ encodes for any of SacA, SacB, SacC, SacD, SacE, SacF, SacG, SacH, SacI, SacJ, Orf1, Orf2, Orf3 or Orf4 proteins (SEQ ID NO:2-15), and variants, mutants or portions thereof which catalyse at least one step of the biosynthesis of safracins.

7. (currently amended) The nucleic acid sequence according to claim 2, wherein the nucleic acid sequence a) ~~which~~ encodes a peptide synthetase, a L-Tyr derivative hydroxylase ~~hidroxylase~~, a L-Tyr derivative methylase, a L-Tyr O-methylase, a methyl-transferase or a monooxygenase or a safracin resistance protein.

8. (original) The nucleic acid sequence according to any one of claims 3-6 wherein the portion is at least 50 nucleotides in length.

9. (original) The nucleic acid sequence according to claim 8 wherein the portion is in the range between 100 to 5000 nucleotides in length.

10. (original) The nucleic acid sequence according to claim 8 wherein the portion is in the range between 100 to 2500 nucleotides in length.

11. (currently amended) A hybridization probe capable of hybridizing under stringent conditions with ~~comprising~~ a nucleic acid sequence according to ~~any one of the preceding claims~~ claim 2.

12. (original) The hybridization probe according to claim 11 which comprises a sequence of at least 10 nucleotide residues.

13. (original) The hybridization probe according to claim 11 which comprises a sequence between 25 to 60 nucleotide residues.

14. (currently amended) ~~Use of a hybridization probe according to any one of claims 11-13 in the detection of a safracin or ecteinascidin gene.~~ A method of detecting a safracin or ecteinascidin

gene comprising hybridizing a probe according to claim 11 with genetic material.

15. (currently amended) The ~~use~~ method according to claim 14 wherein the gene detection is conducted in *Ecteinascidia turbinata*.

16. (withdrawn) A polypeptide encoded by a nucleic acid sequence of any one of claims 2-10.

17. (withdrawn) The polypeptide according to claim 16 which comprises an amino acid sequence selected from the group consisting of SEQ ID NO:2-15.

18. (currently amended) A vector comprising a nucleic acid sequence of ~~any one of claims 2-10~~ claim 2.

19. (original) The vector according to claim 18 which is an expression vector.

20. (original) The vector according to claim 18 which is a cosmid.

21. (currently amended) A host cell transformed with one or more ~~of the~~ nucleic acid sequences according to claim 2 ~~of any one of claims 2-10~~.

22. (currently amended) A host cell comprising a vector of claim 18 ~~any one of claims 18-20~~.

23. (original) The host cell according to claim 22 wherein the host cell is transformed with an exogenous nucleic acid comprising a gene cluster encoding polypeptides sufficient to direct the synthesis of a safracin.

24. (currently amended) The host cell according to claim 22 ~~claims 22 or 23~~ which is a microorganism.

25. (original) The host cell according to claim 24 which is a bacterium.

26. (currently amended) A recombinant bacterial host cell in which at least a portion of a nucleic acid sequence of ~~any one of claims 2-10~~ claim 2 is disrupted to result in a recombinant host cell that produces altered levels of safracin compound or safracin analogue, relative to a corresponding nonrecombinant bacterial host cell.

27. (original) The recombinant cell of claim 26, wherein the disrupted nucleic acid sequence is endogenous.

28. (withdrawn) A method of producing a safracin compound or safracin analogue comprising fermenting an organism in which the copy number of the gene cluster of claim 1 has been increased.

29. (withdrawn) A method of producing a safracin compound or safracin analogue comprising fermenting an organism in which expression of genes encoding polypeptides sufficient to direct the synthesis of a safracin or safracin analogue has been modulated by manipulation or replacement of one or more genes or sequence responsible for regulating such expression.

30. (withdrawn) A method of producing a safracin compound or safracin analogue comprising contacting a compound that is a substrate for a polypeptide encoded by one or more of the open reading frames of the safracin biosynthesis gene cluster of claim 1 with said polypeptide, wherein the polypeptide chemically modifies the compound.

31. (withdrawn) The method according to claims 28 or 29 wherein the organism is *Pseudomonas* sp.

32. (currently amended) A composition comprising at least one nucleic acid sequence ~~of any one of claims 2-10~~ according to claim 2.

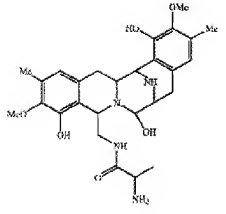
33. (withdrawn) ~~Use of a composition according to claim 32 for the combinatorial biosynthesis of one or more of non-ribosomal peptide synthetases, diketopiperazine rings and safracins.~~ A method of combinatorial biosynthesis comprising use of a composition according to claim 32 for

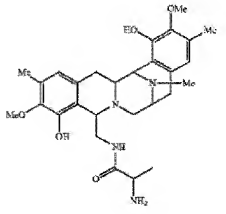
the combinatorial biosynthesis of one or more of non-ribosomal peptide synthetases, diketopiperazine rings and safracins.

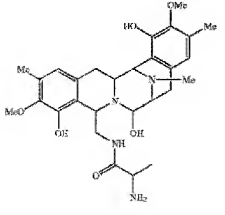
34. (original) Use of P2, P14, analogs and derivatives thereof in combinatorial biosynthesis of one or more of non-ribosomal peptide synthetases, diketopiperazine rings and safracins.

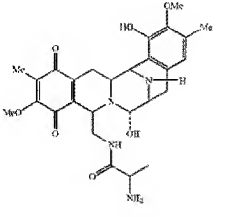
35. (withdrawn) A safracin compound obtainable by a method according to any of claims 28-31.

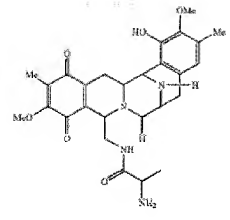
36. (withdrawn) A safracin compound according to claim 35 wherein the compound has one of the following formulas

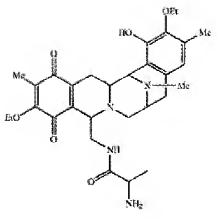


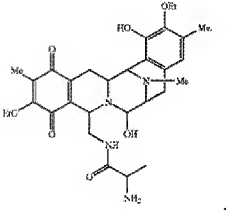












37. (withdrawn) Use of a compound according to claims 35 or 36 as an antitumor agent.

38. (withdrawn) Use of a compound according to claims 35 or 36 in the manufacture of a medicament for the treatment of cancer.

39. (withdrawn) Use of a compound according to claims 35 or 36 as an antimicrobial agent.

40. (withdrawn) Use of a compound according to claims 35 or 36 in the manufacture of a medicament for the treatment of microbial infections.

41. (withdrawn) A pharmaceutical composition comprising a compound according to claims 35 or 36 and a pharmaceutically acceptable diluent, carrier or excipient.

42. (withdrawn) Use of a compound according to claims 35 or 36 in the synthesis of ecteinascidin compounds.

43. (new) The nucleic acid according to claim 2 wherein the nucleic acid sequence a) comprises at least one of the *sacABCDEFGH* or *sacIJ* operons.

44. (new) The nucleic acid sequence according to claim 2, wherein the nucleic acid sequence a) comprises at least one of the *sacA, sacB, sacC, sacD, sacE, sacF, sacG, sacH, sacI, sacJ, orf1, orf2, orf3* or *orf4* genes.

45. (new) The nucleic acid sequence according to claim 2 wherein the nucleic acid sequence a) encodes a polypeptide which catalyses at least one step of the biosynthesis of safracins and is at least 30% identical in amino acid sequence to a polypeptide encoded by any of the safracin gene cluster open reading frames *sacA* to *sacJ* and *orf1* to *orf4*.